Topics in Primary Care Medicine

Evaluation of Hematuria in Adults

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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A small number of erythrocytes may be found in normal urine, but more than three to five erythrocytes per high-power field on a microscopic examination is generally considered abnormal. Hematuria is a common adult problem. In a recent population-based study, 13% of adults had asymptomatic hematuria. There is a general perception that hematuria is a serious problem and that potentially life-threatening causes must be vigorously ruled out. While an aggressive approach is clearly indicated in certain "high-risk" populations (such as the elderly), otherwise asymptomatic adults younger than 40 years rarely have serious occult diseases causing hematuria. In this article I will discuss the causes of hematuria and present an approach to evaluating hematuria for primary care providers.

Causes of Hematuria

Several studies have examined the causes of hematuria and have found that distinctions between gross and microscopic hematuria, or between hematuria present on one or several analyses, cannot be relied on to predict a benign process. Therefore, clinicians must consider the possibility that even a single episode of asymptomatic microscopic hematuria may indicate a serious disease. The frequency of specific causes of hematuria varies widely in currently reported studies, as Table 1 shows. These differences reflect the different methods, patient populations, and referral patterns. Many of these studies are from referred urologic populations and do not represent the patients seen in a primary care setting. Neoplasms, infections, and nephrolithiasis are common causes in these studies. Urethrotrigonitis is a poorly defined group of inflammatory disorders of unclear significance described in the older urologic literature. Many cases of hematuria have no clear cause despite an extensive workup. In the past these have been labeled "benign primary hematuria" or "essential hematuria." Many of these patients have glomerular abnormalities, such as immunoglobulin (Ig) A nephropathy.

In a recent study of patients with asymptomatic microscopic hematuria in a primary care setting, Mohr and coworkers found a low frequency of life-threatening urologic disease. The results of this population-based study should accurately reflect the causes of hematuria found in most primary care settings. Serious urologic disease, which included neoplasms, ureteral calculi, and hydronephrosis, was found in 2.3% of cases, and only 0.5% had bladder or renal carcinoma. Age was a significant risk factor for malignant diseases, and younger patients, particularly those younger than 55, did well over a seven-year observation period. Serious urologic disease was also more common in men than in women. Unfortunately, at this time there are no prospective population-based studies on hematuria to confirm these findings or identify other risk factors for serious disease.

The numerous causes of hematuria can be classified several different ways, and one example is shown in Table 2. The five major etiologic categories are glomerular, renal (nonglomerular), postrenal, hematologic, and false hematuria.

Glomerular

The most common cause of glomerular bleeding is glomerulonephritis. Acute glomerulonephritis, either primary or secondary to a systemic disease, is usually characterized by the sudden appearance of hematuria, proteinuria, and erythrocyte casts. The associated symptoms and selected serologic findings often help differentiate among the various causes of secondary glomerulonephritis, but a renal biopsy may be required to differentiate among the primary types of the disorder.

Primary glomerulonephritis may also present with only isolated hematuria without proteinuria or casts. Many patients with this disorder have been diagnosed as having "benign primary hematuria" in the past when extensive evaluations were unrevealing and the long-term prognosis appeared to be good. If a renal biopsy is done on these patients, as many as 15% reportedly show no abnormalities. A wide variety of lesions are found in the other 85% of cases, and a substantial proportion of these patients are found to have mesangial abnormalities and IgA deposits with immunofluorescent staining. The clinical manifestations of so-called IgA nephropathy range from asymptomatic hematuria following viral infections (Berger's disease) to systemic involvement as seen in Schönlein-Henoch purpura. Treatment is primarily supportive and the long-term prognosis generally good, but

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some patients do require therapy for progressive hypertension or renal insufficiency.

Another cause of hematuria that is thought to be glomerular in origin is strenuous exercise. Exercise-induced hematuria was documented in 18% of male runners in a marathon foot race. It is characterized by gross or, more commonly, microscopic hematuria during or shortly after strenuous exercise. Exercise-induced hematuria persists for 24 to 48 hours after the activity but is not associated with other signs or symptoms of renal disease. Although the bleeding is thought to be glomerular in origin, the long-term prognosis is excellent, and if the findings resolve within 48 hours, most experts agree that no further evaluation is indicated.

TABLE 1.—*Frequency of Common Causes of Hematuria*

Cause of Hematuria	*Frequency, %*
Neoplasm	2-18
Infection	0-24
Nephrolithiasis	4-25
Obstruction	0-3
Trauma	0-3
Glomerulonephritis	0-10
Prostatic hypertrophy	0-23
Urethrotrigonitis	1-24
No diagnosis	10-93

TABLE 2.—*Common Causes of Hematuria**

- Glomerular
  - IgA nephropathy
  - Other glomerulonephritis
  - Alport's syndrome
  - Benign familial hematuria
  - Strenuous exercise
- Renal (nonglomerular)
  - Renal infarct
  - Renal vein thrombosis
  - Tuberculosis
  - Pyelonephritis
  - Polycystic disease
  - Medullary sponge kidney
  - Interstitial nephritis—drug-related, infection, and the like
  - Neoplasm
  - Vascular malformations
  - Trauma
  - Papillary necrosis
- Postrenal
  - Nephrolithiasis
  - Tumors of lower urinary tract
  - Cystitis—infection, drug-related, radiation, idiopathic
  - Prostatitis
  - Foreign bodies of bladder or urethra
  - Urethritis
  - Benign prostatic hypertrophy
  - Obstruction
- Hematologic
  - Coagulopathy
  - Anticoagulation
  - Sickle cell anemia and trait
- False
  - Vaginal bleeding
  - Fictitious
  - Pigmenturia—porphyria, hemoglobinuria, myoglobinuria, food, drugs

*Modified from Abuelo (*Urology* 1983; 21:215-225).

Renal (Nonglomerular)

Nonglomerular renal lesions that may cause hematuria include a variety of disorders such as pyelonephritis, renal infarct, renal vein thrombosis, interstitial nephritis, papillary necrosis, and tumors. Of all renal tumors 90% are renal cell carcinoma, the second most common malignant neoplasm of the urinary tract. Renal cell carcinoma occurs predominantly in older patients; only 4% of cases are found before age 40. Approximately 60% of these cases present with hematuria, but various systemic presentations including hypertension, polycythemia, and fever are common. If these slow-growing tumors are detected early and surgically removed before the tumor reaches the capsule, the five-year survival may be as high as 67%.

Postrenal

Hematuria commonly results from postrenal causes such as nephrolithiasis, cystitis, prostatitis, and lower tract neoplasms, particularly transitional cell carcinoma of the bladder (the most common malignant disorder of the urinary tract). Unfortunately, as many as 22% of cases of transitional cell carcinoma are not associated with detectable hematuria. Again, if detected and treated early, lower urinary tract cancers generally have an excellent prognosis. Although benign prostatic hypertrophy may cause hematuria, other causes must be ruled out because the majority of patients will ultimately have another cause for the hematuria.

Hematologic

Hematologic causes of hematuria include coagulopathies, excessive anticoagulation, and hemoglobinopathies. Therapeutic anticoagulation or antiplatelet therapy generally does not cause hematuria, and underlying disease must be excluded. The sickle cell trait can cause microscopic or gross hematuria. The hematuria is usually painless and resolves spontaneously, but the mechanism is unknown. The sickle cell trait should also be considered in nonblacks as well, as the trait is widely distributed among the populations of southern Europe, the Middle East, North Africa, and India.

False Hematuria

False hematuria includes bleeding from other sources, such as the vagina or external genitalia, and pigmenturia. Pigmenturia is common with certain foods, such as beets, and drugs including phenazopyridine, methyldopa, and rifampin. Myoglobinuria and hemoglobinuria both cause positive urine dipstick tests in the absence of erythrocytes on microscopic examination. Fictitious hematuria can be exceedingly difficult to diagnose and is best ruled out by careful catheterization.

Evaluation

A cost-effective and rational approach to hematuria should always begin with a detailed history. In addition to questions related to the specific causes noted previously, such as recent strenuous exercise or a family history of renal disease, several other historical points are worth pursuing. Gross hematuria at the beginning or end of micturition sug-

gests a urethral or prostatic source. Clots may imply a postglomerular source. If the hematuria was preceded by an upper respiratory tract infection, the interval between symptoms is helpful—in Berger's disease, the hematuria begins with or shortly after an upper respiratory tract infection, but in glomerulonephritis that follows a streptococcal infection, there is a latent period of seven to ten days.

The physical examination should be directed to detect signs of acute glomerulonephritis such as hypertension and volume overload. The abdomen, pelvis, and prostate should be examined for masses or tenderness, and the urethral orifice must be visualized.

The laboratory evaluation of hematuria should be directed toward identifying potentially serious or reversible causes. Unless the findings of the history and physical examination point elsewhere, the initial laboratory evaluation of hematuria should be limited to a urine culture (to rule out subacute or asymptomatic bacterial infections), blood urea nitrogen, serum creatinine levels, and a urinalysis. If renal insufficiency is present, a separate evaluation of that abnormality should be undertaken, including the exclusion of dehydration, infection, and obstruction.

The urinalysis should not be delegated to a laboratory technologist. Urine dipstick tests may occasionally be falsely normal with low but significant levels of hematuria, particularly in the presence of ascorbic acid. The microscopic examination must be done on freshly spun urine to detect formed elements. Pyuria suggests an infectious or inflammatory process. Erythrocyte casts are highly suggestive of glomerulonephritis, and their presence can direct further evaluation. If no erythrocytes are seen, pigmenturia, such as hemoglobinuria or myoglobinuria, may be present.

A urine protein reaction of greater than 1+ on the dipstick in a patient with hematuria may point to a glomerular lesion, and a 24-hour urine collection should be done to quantify the urinary protein. Infrequently, proteinuria may also result from gross hematuria with hemolysis. Although the diagnostic yield is low, an intravenous pyelogram is indicated in patients with substantial proteinuria to rule out the renal causes of hematuria and proteinuria, such as reflux nephropathy, renal tuberculosis, papillary necrosis, and renal cell carcinoma. If the pyelogram is unrevealing, the patient most likely has glomerulonephritis, and an appropriate evaluation should be initiated. If the proteinuria remains unexplained and the protein concentration is greater than 0.15 grams per day (150 mg per day), the patient should be referred to a nephrologist for further evaluation and a possible renal biopsy.

Isolated hematuria, present in a substantial number of patients, is defined as hematuria without other symptoms or evidence of infection, renal insufficiency, or proteinuria. Patients with isolated hematuria have generally undergone a number of additional studies, such as intravenous pyelography and cystoscopy, to rule out serious disorders. This approach is well accepted in adults older than 50 years where the incidence of malignancy is high, but some investigators feel the risk of iatrogenic complications and added cost may outweigh the benefit in young adults. Based on the data of Mohr and others, many young persons with isolated hematuria will be investigated needlessly to find those few with a dangerous and reversible process. The consequences, however, of an undiagnosed malignant lesion in a young adult are serious, even if rare. There is yet no consensus on whether to evaluate isolated hematuria in young adults, and most practitioners are awaiting further studies and the elucidation of risk factors before changing their approach to this problem.

If a clinician decides to further evaluate a patient with isolated hematuria, or if a patient's symptoms warrant additional testing, an intravenous pyelogram, cystoscopy, and urine cytologic examination should be done. A well-done pyelogram is sensitive, at least 95%, in detecting renal anatomic abnormalities that can be further evaluated with sonography, computed tomography, or needle aspiration if necessary. Cystoscopy is considered the best diagnostic test to rule out lower genitourinary tract disease, and it may localize the source of bleeding from one or both ureters. A cytologic examination of voided urine will often detect high-grade bladder tumors. As many as 95% of grade III and invasive bladder tumors are detected by a cytologic examination of three consecutive urine specimens. A cytologic examination is less likely to detect low-grade tumors of the bladder and cannot be used alone to exclude serious disease.

If the above studies are unrewarding, consideration should be given to checking coagulation studies and doing hemoglobin electrophoresis to rule out the sickle trait. First-degree relatives should also have their urine examined to identify hereditary hematuria.

Patients without a specific diagnosis after an appropriate evaluation can be managed in one of several ways. If the bleeding is localized to one kidney and is serious or results in progressive anemia, angiography may be indicated to identify vascular malformations. Episodes of hematuria following upper respiratory tract infections probably represent IgA nephropathy, and the patient should be observed for the development of hypertension or azotemia. If a patient is older than 40 years and has hematuria of an unclear cause, most urologists suggest close follow-up for at least three years with a repeat urinalysis and cytologic examination every six months and yearly cystoscopy and intravenous pyelography.

Additional studies are helpful in certain circumstances. Phase contrast microscopy, if properly done, is able to distinguish erythrocytes of glomerular origin (which display a typical dysmorphism) from those of postrenal sites. Some trained observers can detect this dysmorphism using light microscopy as well. Several studies support the efficacy of phase contrast microscopy, but it has yet to gain widespread use. If IgA nephropathy is present, a biopsy of normal skin reveals IgA deposits in 20% to 50%, and serum IgA levels are elevated in about 50%. Skin biopsy and serum IgA levels are insensitive tests for diagnosing IgA nephropathy and are of use only in confirming suspected cases.

A renal biopsy is of little use in the evaluation of isolated hematuria. In these cases, most glomerular lesions identified do not respond to any current therapy. In addition, the renal biopsy provides little prognostic information in isolated hematuria, as most patients follow a benign course regardless of the histopathology identified.

In summary, hematuria clearly has a multitude of causes, many of which are benign. Referral to a urologist is appropriate if the findings of an intravenous pyelogram or cytologic examination suggest malignancy or if cystoscopy is indicated to rule out lower tract disease. A nephrologist should be consulted if renal insufficiency, acute glomerulo-

nephritis, or significant proteinuria is present. Using a well-reasoned and logical approach, primary care providers are frequently able to define the cause without unnecessary expense or risk to the patient.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Heart Disease in Infants, Children, and Adolescents

Fourth Edition—Edited by Forrest H. Adams, MD, Emeritus Professor of Pediatrics and formerly Head, Division of Cardiology, Department of Pediatrics, University of California, Los Angeles, School of Medicine; George C. Emmanouilides, MD, Professor of Pediatrics, University of California, Los Angeles, School of Medicine, and Chief, Division of Pediatric Cardiology, Harbor-UCLA Medical Center, Torrance, California; and Thomas A. Riemenschneider, MD, Associate Dean; Professor of Pediatrics, Epidemiology, and Biostatistics; and formerly Chief, Division of Pediatric Cardiology, Case Western Reserve University School of Medicine, Cleveland. Williams & Wilkins, 482 E Preston St, Baltimore, MD 21202, 1989. 1,048 pages, price not known.

The latestest edition of *Heart Disease in Infants, Children, and Adolescents* is a substantially enlarged version of a classic textbook on cardiovascular disease in the young patient. The new edition contains 56 chapters by 108 experts encompassing a wide spectrum of topics. The book combines time-proven facts and principles with newer concepts and technology developed in the six years since the third edition was published.

In the General Cardiology section, the noninvasive diagnosis chapter includes two parts on ultrasound, echocardiography and Doppler echocardiography, and a part on magnetic resonance imaging and positron emission tomography, reflecting the increasing prominence of noninvasive imaging in pediatric cardiology. The invasive methods chapter updates standard cardiac catheterization techniques, including a section on indications for surgical procedures without catheterization. The transvascular catheter approach to tissue diagnosis and therapy is discussed by experts on myocardial biopsy and balloon dilatation procedures for stenotic valves and vessels. Techniques for catheter closure of patent ductus arteriosus and intracardiac defects are also evaluated. Other parts discuss electrocardiography, exercise testing, nuclear cardiology, angiocardiography, and electrophysiology.

The Congenital Defects section presents the broad spectrum of congenital disease, with updates on medical and surgical techniques. The Fontan and Norwood operations are of particular interest. An example of the increasing scope of the book is the chapter on the adult with congenital heart disease. Patients with congenital heart disease are surviving into adulthood in increasing numbers, with more complex lesions presenting new challenges to both pediatric and adult cardiologists. The problems of the pregnant young woman with congenital heart disease are given special attention.

Perhaps the most interesting because of its diversity is the Special Problems section, which addresses 18 different topics. In addition to the problems of adults and pregnancy mentioned above, prenatal diagnosis of congenital anatomic disease and dysrhythmias; hypertension, both pulmonary and systemic; cardiomyopathy, shock, surgical techniques, and transplantation are discussed. There are new chapters on psychosocial and ethical considerations—important problems in pediatric cardiology because of the high risk to many patients and high financial cost for diagnosis and treatment.

Other sections address infectious disease, metabolic and nutritional problems, and cardiac disease as part of a systemic illness. The continuing problem of infectious endocarditis, the resurgence of rheumatic disease, and new knowledge of metabolic diseases emphasize the value of these sections.

This large text is a valuable reference for the physician with a special interest in cardiovascular disease in the young. It is neither a condensed version of pediatric cardiovascular disease suitable for rapid review nor does it replace the several excellent journals reporting newer investigations. The book does present a huge fund of information, with an excellent bibliography evaluated by clinicians and scientists who are experts in the areas they represent. In this category the fourth edition is one of the best textbooks available.

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